As amended, the indicated claims include the following changes, made in response to the specific rejections made by the Examiner:

a) Claims 11-15 are rejected "as being incomplete in Claim 11 for omitting essential steps, such omission amounting to a gap between the steps". In particular, the Examiner alleges that the omitted steps are "the steps reciting 'conditions appropriate' for training Drosophila to induce transcription-dependent memory and the steps reciting 'conditions insufficient' for training Drosophila to induce transcription-dependent memory." Applicants respectfully disagree with this assessment.

The test for definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification. Orthokinetics, Inc. v. Safety Travel Chairs, Inc., 1 U.S.P.Q.2d 1081, 1088 (Fed. Cir. 1986). If the claims read in light of the specification reasonably appraise those skilled in the art of the scope of the invention, § 112 demands no more. Hybritech, Inc. v. Monoclonal Antibodies, Inc., 231 U.S.P.Q. 81 (Fed. Cir. 1987), *cert. denied*, 480 U.S. 947 (1987).

As defined in the specification, "conditions appropriate" for training Drosophila to induce transcription-dependent memory formation refer to experimental conditions that are used to induce transcription-dependent memory in Drosophila (see, e.g., page 9, lines 11-13). Applicants disclose that transcription-dependent memory formation can be induced in Drosophila using a spaced training protocol (see, e.g., page 6, lines 12-13). Specific examples of spaced training protocols are provided (see, e.g., page 6, lines 12-13; and page 10, lines 7-11). Other experimental conditions that can be used to induce transcription-dependent memory in Drosophila can be determined using art-known methods.

As defined in the specification, "conditions insufficient" for training Drosophila to induce transcription-dependent memory refer to experimental conditions that are used to induce transcription-independent memory but not transcription-dependent memory in Drosophila (see, e.g., page 5, lines 17-19; page 6, lines 9-11; page 9, lines 13-14). Applicants disclose that transcription-independent memory formation can be induced in Drosophila using a massed training protocol (see, e.g., page 6, lines 14-15). Specific examples of massed training protocols

are provided (see, e.g., page 6, lines 14-15; and page 10, lines 4-6 of the specification). Other experimental conditions that can be used to induce transcription-independent memory but not transcription-dependent memory in Drosophila can be determined using art-known methods.

Thus, it is respectfully submitted that essential steps are not omitted from Claim 11. Accordingly, one skilled in the art would find Claims 11-15 to be complete and the metes and bounds clear when read in light of the specification.

Notwithstanding the above, step (a) of Claim 11 has been amended to delete the phrase "under conditions appropriate" and step (f)(i) has been amended to replace "under appropriate conditions ... insufficient to induce transcription-dependent memory" with "to induce transcription-independent memory formation but not transcription-dependent memory formation". This amendment is not intended to narrow the scope of the claims.

e) Claim 14 is rejected "as being incomplete for omitting essential steps, such omission amounting to a gap between the steps." In particular, the Examiner alleges that the omitted steps are "the steps reciting 'conditions sufficient to induce transcription-independent memory but not transcription-dependent memory'". Although Applicants disagree with the Examiner's assessment for the reasons of record, in an effort to advance the prosecution of the subject application, Claim 14 has been cancelled. The dependency of Claim 15 has been appropriately changed to reflect this cancellation of Claim 14.

f) Claims 24-26 are rejected "as being incomplete in Claim 24 for omitting essential steps, such omission amounting to a gap between the steps". In particular, the Examiner alleges that the omitted steps are "the steps reciting 'conditions appropriate' for training Drosophila to induce transcription-dependent'" memory. Applicants respectfully disagree with this assessment.

As discussed above, "conditions appropriate" for training Drosophila to induce transcription-dependent memory refer to experimental conditions that are used to induce transcription-dependent memory in Drosophila (see, e.g., page 9, lines 11-13). Applicants disclose that transcription-dependent memory formation can be induced in Drosophila using a spaced training protocol (see, e.g., page 6, lines 12-13). Specific examples of spaced training

protocols are provided (see, e.g., page 6, lines 12-13; and page 10, lines 7-11). Other experimental conditions that can be used to induce transcription-dependent memory in Drosophila can be determined using art-known methods. Thus, it is respectfully submitted that essential steps are not omitted from Claim 24. Accordingly, one skilled in the art would find Claims 24-26 to be complete and the metes and bounds clear when read in light of the specification.

Notwithstanding the above, step (a) of Claim 24 has been amended to delete the phrase "under conditions appropriate". This amendment is not intended to narrow the scope of the claims.

Paragraph 7: Rejection of Claims 11-15 and 24-26 Under 35 U.S.C. § 103(a)

Claims 11-15 and 24-26 have been rejected under 35 U.S.C. § 103(a) as being obvious over Yin *et al.* (*Cell*, 79:49-58 (1994)) in view of Ramsey *et al.* (*Nature Biotechnology*, 16:40-44 (1998)) and Tully *et al.* (U.S. Patent No. 5,929,223).

Teachings of the Cited References

Yin *et al.*

Yin *et al.* teach the use of a dominant negative CREB transgene to investigate the role of CREB in long term memory (LTM) formation in Drosophila. In particular, Yin *et al.* teach the use of the inducible transgene approach in combination with training protocols for inducing memory formation to investigate the effect of inducing a dominant negative CREB transgene on LTM formation. More specifically, Yin *et al.* teach the production of transgenic flies that express *dCREB2-b* under the control of a heat-shock promoter (*hs-dCREB2-b* transgene), training the transgenic flies which had been heat-shock induced or left uninduced, under conditions appropriate to induce memory formation in the flies, extracting RNA from the head tissue of trained flies, exposing the extracted RNA to a dCREB2-b cDNA fragment under conditions appropriate for hybridization of dCREB2-b transgene RNA to the dCREB2-b cDNA fragment and detecting hybridization of dCREB2-b transgene RNA to the dCREB2-b cDNA

fragment. The hybridization signal detected using RNA extracted from the heads of trained transgenic flies is compared to the hybridization signal detected using RNA extracted from the heads of wildtype flies (i.e., flies that do not include the *hs-dCREB2-b* transgene) trained in the same manner as the transgenic flies (Yin *et al.*, page 50, Figure 1A).

Yin *et al.* also disclose the results of behavioral experiments in which the performance index of the trained flies is measured (Yin *et al.*, page 51, column 2 to page 53, column 2) and provide methods for statistically analyzing the behavioral data obtained (Yin *et al.*, page 55, column 2, second paragraph from bottom ("Statistical Analyses of Behavioral Data") to page 56, column 2, fourth full paragraph ("Shock Reactivity in rsh;17-2 Files (Table 1)").

Yin *et al.* do not teach or suggest the use of microarray chips in a method to identify genes involved in transcription-dependent memory formation. Also, Yin *et al.* do not teach or suggest the use of a statistical comparison between signal detected from a control microarray chip and signal detected on a microarray chip using cDNA probes synthesized from RNA extracted from head tissue of Drosophila trained under conditions appropriate to induce transcription-dependent memory to identify genes involved in transcription-dependent memory formation.

Tully *et al.*

Tully *et al.* is cited by the Examiner as teaching "the method wherein the hybridization signals from the spaced trained and massed trained Drosophila are compared." In particular, the Examiner contends that in column 25, lines 6-30, Tully *et al.* teach:

> training two groups of Drosophila, one under conditions to induce transcription-dependent memory and a second under condition insufficient to induce transcription-dependent memory, extracting RNA from head tissue of both groups, hybridizing the RNA to DNA sequences from genes of the Drosophila and comparing the hybridization signals between the two groups.

Paper No. 10, at page 7, lines 6-11. Respectfully, it appears that the Examiner may have misunderstood the cited passage. It is noted that Example 2, which includes column 25,

lines 6-30, is the same as or similar to the "Experimental Procedures" (pages 55 to 57) and "Results" (pages 50 to 53) sections of the Yin *et al.* reference.

At column 25, lines 6-30, Tully *et al.* disclose the method for performing Northern analysis, which is the same as or similar to the method disclosed by Yin *et al.* (see Yin *et al.*, at page 56, column 2, last paragraph). At column 26, lines 9-15, Tully *et al.* report the results revealed by Northern analysis, which are the same as or similar to the results reported by Yin *et al.* (see Yin *et al.*, at page 50, column 2, last paragraph).

Similarly, in Example 2, Tully *et al.* teach the use of a dominant negative CREB transgene to investigate the role of CREB in LTM formation in Drosophila. In particular, Tully *et al.* teach the use of the inducible transgene approach in combination with training protocols for inducing memory formation to investigate the effect of inducing a dominant negative CREB transgene on LTM formation. More specifically, Tully *et al.* teach the production of transgenic flies that express *dCREB2-b* under the control of a heat-shock promoter (*hs-dCREB2-b* transgene), training the transgenic flies which had been heat-shock induced or left uninduced, under conditions appropriate to induce memory formation in the flies, extracting RNA from the head tissue of trained flies, exposing the extracted RNA to a dCREB2-b cDNA fragment under conditions appropriate for hybridization of dCREB2-b transgene RNA to the dCREB2-b cDNA fragment and detecting hybridization of dCREB2-b transgene RNA to the dCREB2-b cDNA fragment. The hybridization signal detected using RNA extracted from the heads of trained transgenic flies is compared to the hybridization signal detected using RNA extracted from the heads of wildtype flies (i.e., flies that do not include the *hs-dCREB2-b* transgene) trained in the same manner as the transgenic flies (Tully *et al.*, column 3, lines 36-41; and Figure 9A).

In Example 2, Tully *et al.* also disclose the results of behavioral experiments in which the performance index of the trained flies is measured (Tully *et al.*, column 26, line 52 to column 28, line 41) and provide methods for statistically analyzing the behavioral data obtained (Tully *et al.*, column 23, line 1 to column 25, line 5).

Tully *et al.* do not teach or suggest the use of microarray chips in a method to identify genes involved in transcription-dependent memory formation. Also, Tully *et al.* do not teach or suggest the use of a statistical comparison between signal detected from a control microarray

chip and signal detected on a microarray chip using cDNA probes synthesized from RNA extracted from head tissue of Drosophila trained under conditions appropriate to induce transcription-dependent memory to identify genes involved in transcription-dependent memory formation.

Ramsey

Ramsey is a 1998 review article describing the state of the art of DNA chip technology, including its successful application "to the simultaneous expression of many thousands of genes and to large-scale gene discovery" (Ramsey, page 40, abstract). For example, Ramsey reports the successful use of DNA arrays to measure differential gene expression in plants, yeast and human samples (Ramsey, page 41, column 1).

Ramsey does not teach or suggest performing a gene chip identification of those genes expressed during transcription-dependent memory formation but not during transcription-independent memory formation or performing a statistical analysis of the gene chip identification output to yield a set of genes that are involved in transcription-dependent memory formation.

The Combination of References

In support of the rejection, the Examiner alleges that it would have been prima facie obvious "to modify the northern blot gene identification of Yin et al. with the microarray identification exhibiting 10 fold sensitivity when compared to Northern Blots as taught by Ramsey wherein multiple response-specific genes are identified for the expected benefit of large-scale, rapid identification of expression-specific genes as taught by Ramsey" (Paper No. 10, at page 6, lines 17-22; and page 8, line 23 to page 9, line 3) and "to modify the RNA analysis of Yin et al. wherein hybridization signals from trained and untrained Drosophila are compared to further compare hybridization signals from Drosophila following the different training protocols as taught by Tully et al. for the obvious benefit of analyzing training-specific expression to thereby identify memory-specific expression" (Paper No. 10, at page 7, lines 11-15.).

Applicants respectfully submit that this rejection is improper because the Examiner has not identified a suggestion in the prior art of the desirability of the proposed combination of references. Combining the elements of separate references which do not themselves suggest the combination necessary to obtain a claimed invention is generally improper. ACS Hospital Systems, Inc. v. Montefiore Hospital, 221 U.S.P.Q. 929, 933 (Fed. Cir. 1984). The only document of record which suggests the desirability of the proposed combination is Applicants' specification. However, the use of the present specification as an instruction manual or template to piece together the teachings of the prior art is impermissible hindsight.

Notwithstanding the above, a *prima facie* case of obviousness is established only if the teachings of the cited art would have suggested the claimed invention to one of ordinary skill in the art with a reasonable expectation of successfully achieving the claimed results. In re Vaeck, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Both the suggestion and the reasonable expectation of success must be found in the prior art, not Applicants' disclosure. Id.

The Court of Appeals for the Federal Circuit has stated that "[t]he proper approach to the obviousness issue must start with the claimed invention *as a whole*." See, e.g., Kimberley-Clark Corp. v. Johnson & Johnson Co., 223 U.S:P.Q. 603, 609 (Fed. Cir. 1984). See also Lindemann Maschinenfabrik G.m.b.H. v. American Hoist & Derrick Co., 221 U.S.P.Q. 481, 488 (Fed. Cir. 1984). It is not proper to pick and choose among individual elements of assorted prior art references to recreate the claimed invention. Smithkline Diagnostics Inc. v. Helena Laboratories Corp., 8 U.S.P.Q.2d 1468, 1475 (Fed. Cir. 1988); Akzo N.V. v. International Trade Comm., 11 U.S.P.Q.2d 1241, 1246 (Fed. Cir. 1986).

The claimed invention pertains to methods of identifying a gene or genes involved in transcription-dependent memory in Drosophila comprising training Drosophila to induce transcription-dependent memory formation in the Drosophila; extracting RNA from head tissue of the trained Drosophila; synthesizing labeled cDNA probes complementary to the extracted RNA extracted; hybridizing the synthesized DNA probes to microarray chips containing DNA sequences from genes of the Drosophila genome under conditions appropriate for hybridization of the DNA probes to complementary DNA sequences on the microarray chips, wherein a signal is produced upon hybridization of the probes to complementary DNA sequences; detecting the

signal produced; and performing a statistical comparison between the detected signal and the signal detected in a control (Claims 11-13, 15 and 24-26). In some embodiments of the invention, control Drosophila are trained under conditions insufficient to induce transcription-dependent memory formation (Claims 11-13 and 15), but sufficient to induce transcription-independent memory formation (Claim 15). In other embodiments of the invention, control Drosophila are naïve (untrained) flies (Claims 24-26). In a particular embodiment of the invention, transcription-dependent memory formation is long term memory formation (Claims 12 and 25). In some embodiments of the invention, transcription-dependent memory formation is induced using a spaced training protocol (Claims 13 and 26) and transcription-independent memory formation is induced using a massed training protocol (Claim 15). The fact that an individual element and/or feature can be located in the prior art does not support the conclusion that the claimed invention as a whole is *prima facie* obvious.

None of the cited references, alone or in their various combinations, would have suggested the claimed invention to one of ordinary skill in the art at the time the invention was made with a reasonable expectation of success. As discussed above, Yin *et al.* and Tully *et al.* teach the use of the inducible transgene approach in combination with training protocols for inducing memory formation to investigate the effect of inducing a dominant negative CREB transgene on long term memory formation. Neither the Yin *et al.* reference nor the Tully *et al.* patent teaches or suggests the use of microarray chips in a method to identify genes involved in transcription-dependent memory formation. In addition, neither the Yin *et al.* reference nor the Tully *et al.* patent teaches or suggests performing a statistical comparison between signal detected from a control microarray chip and signal detected on a microarray chip using cDNA probes synthesized from RNA extracted from head tissue of Drosophila trained under conditions appropriate to induce transcription-dependent memory to identify genes involved in transcription-dependent memory formation.

Ramsey does not cure the deficiencies of the Yin *et al.* and Tully *et al.* references. Although Ramsey teaches the use of microarray chips in a method of detecting differential expression of genes, Ramsey does not teach or suggest performing a gene chip identification of those genes expressed during transcription-dependent memory formation but not during

transcription-independent memory formation or performing a statistical analysis of the gene chip identification output to yield a set of genes that are involved in transcription-dependent memory formation.

Accordingly, the cited references, either alone or in their various combinations, would not have reasonably suggested the claimed invention to one of ordinary skill in the art, at the time the invention was made, with a reasonable expectation of success. The cited references merely indicate that isolated elements and/or features recited in the claims are known. This is insufficient to render the claimed invention *prima facie* obvious.

Reconsideration and withdrawal of this rejection of the claims under 35 U.S.C. § 103(a) are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 341-0036.

Respectfully submitted,

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Dated: January 14, 2002

MARKED UP VERSION OF AMENDMENTS

Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

11. (Twice Amended) A method of identifying a gene or genes involved in transcription-dependent memory comprising the steps of:

(a) training Drosophila [under conditions appropriate] to induce transcription-dependent memory formation in said Drosophila;

(b) extracting RNA from head tissue of Drosophila trained in step (a);

(c) synthesizing labeled cDNA probes complementary to the RNA extracted in step (b);

(d) hybridizing the DNA probes synthesized in step (c) to microarray chips containing DNA sequences from genes of the Drosophila genome under conditions appropriate for hybridization of the DNA probes to complementary DNA sequences on the microarray chips, wherein a signal is produced from said labeled probes upon hybridization of said probes to complementary DNA sequences;

(e) detecting the signal produced in step (d); and

(f) performing a statistical comparison between the signal detected in step (e) and the signal detected in a control for each gene, wherein said control is obtained according to a method comprising the steps of:

(i) training control Drosophila [under appropriate conditions, wherein said conditions are insufficient] to induce transcription-independent memory formation but not transcription-dependent memory formation in said control Drosophila;

(ii) extracting RNA from head tissue of said control Drosophila trained in step (f)(i);

(iii) synthesizing labeled cDNA probes complementary to the RNA extracted in step (f)(ii); and

(iv) hybridizing the DNA probes synthesized in step (f)(iii) to microarray chips containing DNA sequences from genes of the Drosophila genome under

conditions appropriate for hybridization of the DNA probes to complementary DNA sequences on the microarray chips, wherein a signal is produced from said labeled probes upon hybridization of said probes to complementary DNA sequences.

15. (Amended) The method of Claim [14] 11 wherein transcription-independent memory formation is induced using a massed training protocol.

24. (Twice Amended) A method of identifying a gene or genes involved in transcription-dependent memory comprising the steps of:

(a) training Drosophila [under conditions appropriate] to induce transcription-dependent memory formation in said Drosophila;

(b) extracting RNA from head tissue of Drosophila trained in step (a);

(c) synthesizing labeled cDNA probes complementary to the RNA extracted in step (b);

(d) hybridizing the DNA probes synthesized in step (c) to microarray chips containing DNA sequences from genes of the Drosophila genome, wherein a signal is produced from said labeled probes upon hybridization of said probes to complementary DNA sequences;

(e) detecting the signal produced in step (d); and

(f) performing a statistical comparison between the signal detected in step (e) and the signal detected in a control for each gene, wherein said control is obtained according to a method comprising the steps of:

(i) extracting RNA from head tissue of control Drosophila;

(ii) synthesizing labeled cDNA probes complementary to the RNA extracted in step (f)(i); and

(iii) hybridizing the DNA probes synthesized in step (f)(ii) to microarray chips containing DNA sequences from genes of the Drosophila genome, wherein a signal is produced from said probes upon hybridization of said probes to complementary DNA sequences.